Novel Biomarkers of Chronic Obstructive Pulmonary Disease (COPD)

The National Heart, Lung, and Blood Institute (NHLBI) invites applications for research grants to identify novel biomarkers of chronic obstructive pulmonary disease (COPD). COPD is a complex group of conditions associated with progressive airway obstruction for which no disease-modifying therapy is currently known. The purpose of this request for applications (RFA) is to promote the identification and characterization of biomarkers that might eventually be useful for studies of COPD pathogenesis, diagnosis, therapeutic stratification of patients, or testing of potential drug treatments. Such biomarkers might reflect the presence or severity of COPD, the rate of disease progression, or exacerbations of the disease. A variety of techniques might be employed, ranging from chemical assays of exhaled air condensate, to proteomic analysis of blood, to functional imaging of lungs by positron emission tomography. The focus of this RFA is on novel biomarkers for COPD that can be determined by minimally invasive means.

Proposed studies must involve characterizations of human subjects and must include individuals who have COPD. Studies of individuals with alpha-1 antitrypsin deficiency will be allowed. It is expected that studies will attempt to correlate particular biomarkers with specific aspects of COPD.

Measurements of multiple biomarkers in individual subjects and testing of multivariate correlations are encouraged. However, applicants should explain their rationale for the choice of each putative biomarker, clearly define the aspect of COPD that is hypothesized to be correlated with the biomarker, and justify the selection of the human subjects to be studied in the context of the underlying hypothesis. Plans for subject recruitment and characterization should be described in detail. The use of previously characterized cohorts of subjects is encouraged, particularly for studies attempting to correlate biomarkers with the rate of disease progression.

It is recognized that certain characterizations of human subjects that might be obtained through this RFA could also serve as phenotypes in studies testing associations of candidate gene polymorphisms with COPD. While it is not the intent of this RFA to support genetic studies, funds may be requested for the collection and storage of DNA specimens. Funds will not be provided for genotyping of study participants. Any applicant wishing to make use of this option must describe briefly the planned use of study data and DNA specimens, specify what costs for DNA collection and storage are included in the proposed budget, and obtain institutional review board approval for the collection and storage of these biological specimens.

The NHLBI intends to commit approximately $3.5 million in fiscal year 2002 to fund 8–10 new grants in response to this RFA. An applicant may request a project period of up to four years and a budget for direct costs of up to $350,000 per year.

The deadline for letters of intent is 25 January 2002, with final applications due 26 February 2002. This RFA will use the NIH Research Project (R01) award mechanism. Further information is available online at http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-02-005.html.

Contact: Tom Croxton, Division of Lung Diseases, NHLBI, 6701 Rockledge Drive, Room 10208, MSC 7952, Bethesda, MD 20892-7952 USA, 301-435-0202, fax: 301-480-3557, e-mail: croxtont@nhlbi.nih.gov. Reference: RFA No. RFA-HL-02-005

Development of Novel Technologies for *in Vivo* Imaging

The National Cancer Institute (NCI) and the NIEHS invite applications for the development of novel image acquisition or enhancement methods, which may incorporate limited pilot or clinical feasibility evaluations using either preclinical models or clinical studies. This initiative is intended to facilitate the proof of feasibility and development of novel imaging technologies for early detection, screening, diagnosis, or image-guided treatment of cancer (NCI) and environmentally induced diseases (NIEHS), and to facilitate clinical evaluation studies of the development that are specifically limited to proof of concept. The National Institute of Biomedical Imaging and Bioengineering may accept assignments of grant applications that address development of novel imaging technologies that are not organ- or disease-specific.

The motivation for this program announcement (PA) is that current technologies for the molecular analysis of disease are largely restricted to *in vitro* methods and need to be extended to the *in vivo* situation. Furthermore, development of molecular probes or tracers for imaging molecular events in preclinical and clinical investigations is essential for detection of molecular changes *in vivo*. Development of innovative high-resolution imaging methods at the cellular or molecular scales is needed, with particular emphasis on identification and characterization of processes in the early formation of disease or early molecular changes during intervention or therapy. Integrations of these emerging molecular imaging methods with advances in traditional imaging methods are also required for more effective *in vivo* investigations of environmentally induced disease and cancer.

Specific emphasis of this PA is directed at 1) the development of highly innovative image acquisition and enhancement methods, including high risk/high gain research on technologies that exploit our knowledge of the molecular basis of cancer and environmentally induced diseases, and 2) the development of other novel imaging methods and the integration of these technologies with emerging molecular imaging methods, where appropriate, for more effective health care delivery. The following objectives would make appropriate topics for proposed projects. This list is not meant to be all-inclusive.

1) *Imaging to detect early changes:* Development of innovative high-resolution imaging methods at the cellular or molecular scales is encouraged, with a particular intent to identify and characterize premalignant abnormalities or early changes preceding the development of other diseases. Novel solutions for *in vivo* microscopic imaging systems or microscopic implanted devices with high spatial, contrast, and temporal resolution are encouraged. Similarly, developments of contrast enhancement methods and imaging probes are also encouraged. Proposed imaging methodologies that emphasize analysis of molecular events on the path to disease are encouraged.

2) *Large-scale screening applications for cancer and environmentally induced disease:* Development and optimization of efficient, low-cost imaging systems for rapid and automated large-scale screening with the intent of achieving significantly higher sensitivity and specificity for disease detection is encouraged. Applications could address significant innovative improvements to current imaging methods or new emerging imaging systems. Research topics of interest include technologies for molecular imaging, means to significantly reduce imaging time or motion effects, use of novel contrast agents or imaging probes, and use of technologies that do not involve ionizing radiation. System integration could include a variety of image processing techniques including temporal analysis of serial studies, close to real-time image processing, novel image display methods, and related imaging informatics and information reduction methods for more cost-effective solutions for screening.

3) *Imaging for diagnosis, staging, or monitoring the effects of therapy:* This initiative encourages the development of novel imaging methods such as functional or molecular imaging or spectroscopy methods that would significantly improve the specificity of diagnosis of cancer and environmentally induced disease, allow deterministic methods or patient-specific staging, or measure early effects of therapy. Examples of system integration would include image fusion or registration from the different modalities employed, development of software methods that would estimate the probability of malignancy or other specific disease identification, quantitative information for monitoring the effects of therapy, and close to real-time image analysis.

4) *Image-guided biopsy (IGB), image-guided therapy (IGT), and interventional procedures:* Novel approaches using imaging technologies are needed to significantly improve specificity, identify lesion extent and microscopic involvement, and minimize the tissue damage accompanying biopsy and therapy. Of particular interest are innovative approaches to IGB, IGT, or interventional methods that include novel imaging systems that provide information at the cellular or molecular level. Examples of system integration that are of interest include, but are not limited to, navigational systems, registration methods for several imaging modalities, real-time feedback mechanisms for controlling therapy, and methods that are adaptive or allow patient-specific optimization of treatment and computer-assisted surgery.

This PA will utilize the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) mechanisms, designed to encourage technology development by eligible small businesses. This PA must be read in conjunction with the current Omnibus Solicitation of the National Institutes of Health, Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Grant Applications (http://grants.nih.gov/grants/funding/sbirsttr1/index.pdf).

The deadlines for letters of intent are 11 February 2002 and 11 June 2002, with final applications due 18 March 2002 and 16 July 2002. More information on this PA is available online at http://grants.nih.gov/grants/guide/pa-files/PAR-01-102.html.

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Technologies for Closing DNA Sequence Gaps and Improving Methods for Obtaining the Sequence of Difficult-to-Sequence Regions

The National Human Genome Research Institute (NHGRI) invites applications to develop strategies and technologies for obtaining DNA sequence in the gaps that, due to limitations in available cloning and sequencing technology, will remain in essentially finished genomic sequence. Such gaps may arise from an inability to clone a region in any available vector system or to obtain sequence from all or part of an available clone. Such gaps have been encountered in every large genome sequencing effort to date. NHGRI encourages the development of novel approaches to allow completion of the DNA sequence within the gaps left by current sequencing methods and to improve the efficiency of sequencing in genomic regions that have proved difficult to sequence.

The large-scale sequencing centers have provided lists of clones containing regions with gaps or DNA that was difficult to sequence, posted at http://www.nhgri.nih.gov/About_NHGRI/Der/gapPA.html. Investigators applying for this program announcement (PA) may use this information to find clones on which they may develop and demonstrate their strategy/technology. This PA is limited to proposals to develop and obtain proof of principle for new technologies.

Approximately $2 million is available for funding, and 5–10 awards may be made during the first year of the program, contingent upon the availability of funds and receipt of a sufficient number of high-quality applications. The anticipated award dates are 1 December 2001, 1 April 2002, and 1 July 2002. This PA will be in effect for three years; additional announcements to continue this program may be issued in the future.

Applications are to be submitted on the grant application form PHS 398 (rev. 4/98) and submitted by the standard deadlines as indicated in the application kit. This form is available online at http://grants.nih.gov/grants/funding/phs398/phs398.html. Applicants planning to submit an investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended/revised version of the preceding grant application types requesting $500,000 or more in direct costs for any year must contact the institute program staff before submitting the application, i.e., as plans for the study are being developed. The applicant must also obtain agreement from the institute staff that the institute will accept the application for consideration, and identify, in a cover letter, the staff member and institute who agreed to accept assignment of the application. More information on this PA is available online at http://grants.nih.gov/grants/guide/pa-files/PAS-00-112.html.

Contact: Jane Peterson, NHGRI, 31 Center Drive, Room B2B07, Building 31, MSC 2033, Bethesda, MD 20892 USA, 301-496-7531, fax: 301-480-2770, e-mail: jane_peterson@nih.gov. Reference: PA No. PAS-00-112

Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses

Discovery and development of new drugs and biologicals for cancer treatment, including gene therapy and drug delivery approaches, normally involves lengthy and costly projects. The multiple components of the overall process including discovery, efficacy testing, development of lead agents, toxicology and pharmacology, investigational new drug application filing, and clinical evaluation may require years and several million dollars. The small business community is an active participant in the cancer therapy discovery effort. Thus it is important that their innovative ideas be supported. The Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs were developed to support innovative research with a commercial intent by small businesses. This program announcement (PA) provides a flexible system within the SBIR and STTR programs to accommodate the special needs of the complex discovery and development process, at least partially, from basic discovery through proof-of-principle demonstration in clinical trials. It is hoped that this initiative will stimulate drug discovery research efforts in the small business community.

This PA must be read in conjunction with the 2001 omnibus solicitation for the NIH SBIR and STTR grant applications, found online at http://grants.nih.gov/grants/funding/sbirsttr1/index.pdf. All of the instructions within the omnibus solicitation apply with the following exceptions: 1) special receipt dates, 2) initial review convened by the Division of Extramural Activities, National Cancer Institute, 3) additional review considerations, 4) more flexible time and budget specifications, and 5) no modular format. Instructions for detailed budgets will be followed.

This PA provides a flexible funding mechanism with regard to budgets and time of award to support the research activities necessary for small businesses to bring their efforts for drug discovery and development to clinical validation. Projects submitted in response to this PA should focus on discovery and development of a specific agent or class of agents. Applications devoted to topics relating more generally to drug discovery such as technology and model development without direct relevance to development of a specific agent are not appropriate.

Flexibility within the PA allows for projects to be presented at all stages of the drug discovery and development process. Projects will be evaluated on overall innovation, strength of the drug discovery approach, and probability of clinical success, with less emphasis on the nature of the specific stage proposed in the application. This latter aspect is especially important if applications are focused on later stages of the drug discovery and evaluation process that may be more routine and often considered less innovative as standalone projects.

The deadline for letters of intent is 6 March 2002, with final applications due 12 November 2002. Institute policy requires that all applicants requesting greater than $500,000 direct costs in any one year must obtain approval from program staff prior to submission of the application. If more than $500,000 per year is requested, this fact must be clearly stated and approval requested in the letter of intent.

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Research on Research Integrity

The Office of Research Integrity, the National Institute of Neurological Disorders and Stroke, and the National Institute of Nursing Research invite applications to support research on research integrity. Research integrity is a vital component of both the reliability of the research record and the trust that underlies public support for research. Therefore, the responsible expenditure of public funds for research must include attention to research integrity. The purpose of the proposed grant program is to foster empirical research on the institutions, processes, and values that affect integrity in research. The sponsoring agencies are particularly interested in studies that will inform policy making at the Department of Health and Human Services, the NIH, and research institutions, with the goal of fostering appropriate attention to integrity in publicly funded research programs.

This request for applications seeks to address the need for more and better information on the factors that encourage and/or discourage integrity in publicly funded research. For our purposes, *research* is defined broadly to include societal, institutional, and individual aspects of the enterprise. *Integrity* is understood as adherence to rules, regulations, guidelines, and commonly accepted professional codes or norms. Applicants are encouraged to submit proposals that will provide generalizable empirical knowledge about the ways in which researchers and research institutions meet or fail to meet their professional responsibilities in the conduct, evaluation, and reporting of research. Particular areas of interest include but are not limited to 1) research norms and/or practices, 2) institutional climate and responsibility, 3) education on the responsible conduct of research, 4) mentor/trainee relationships, 5) data acquisition, management, sharing, and ownership, 6) responsible authorship, 7) integrity of publication practices and the research record, 8) research collaborations and issues that may arise from such collaborations, 9) conflicts of interest, and 10) the meaning of research misconduct and the regulations, policies, and guidelines that govern research misconduct in Public Health Service–funded institutions.

Applicants should use the NIH individual research project grant (R01) award mechanism. Prospective applicants are asked to submit a letter of intent by 15 October 2001, with final applications due 19 November 2001. More information is available on the Internet at http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-02-005.html.

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